## REMARKS

This is meant to be a complete response to the Office Action mailed June 6, 2007. In the Office Action, the Examiner objected to claims 7-8 and 22-23. The Examiner also rejected claims 1, 3-11, 19 and 21-23 under 35 U.S.C. 112, ¶1, and rejected claims 3 and 21 under 35 U.S.C. 112, ¶2. The Examiner also rejected Applicant's claims 1, 3-11, 19 and 21-23 under 35 U.S.C. 103(a) as being obvious over the combined teachings of Rosenberg (US 5,158,976) with evidence provided by Melzack et al. (1965) and further in view of Fujimoto et al. (US 6,291,523).

### Applicant's Response to the Objection to the Claims

In the Office Action, the Examiner objected to claims 7-8 and 22-23, and stated that he believed a comma was missing from the first line of each claim.

Claims 7-8 and 23 have been amended herein to add the requested comma thereto; however, Applicant respectfully submits that claim 22 is grammatically correct, and that the comma in the first line therein is appropriately placed after the term "wherein", as such term is followed by an "in the step" clause.

Therefore, Applicant respectfully requests reconsideration and withdrawal of the objection to the claims as now amended.

Applicant's Response to the 35 U.S.C. 112, ¶1 Rejections

In the Office Action, the Examiner rejected Applicant's claims 1, 3-11, 19 and 21-23 under 35 U.S.C. 112, ¶1, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In support thereof, the Examiner stated that:

> the specification, while enabling for alleviating the chronic pain in an individual via administering a glutaminase inhibitor to said individual does not provide information on inhibition of glutaminase enzyme production by said step. Also, the specification as currently presented, apart from merely mentioning, does not disclose oral administration of said glutaminase inhibitor. Specification as currently presented, merely shows a statement that "One specific example of a compound functioning in this manner is dicoumarol (DC), which is shown herein to inhibit ZC activity and thus inhibit GT production, thereby relieving pain. Therefore, the terms "glutaminase inhibitor", "inhibitor of glutaminase enzyme activity" and "inhibitor of glutaminase synthesis" can all be used interchangeably herein" (Specification, Page 18, Line 15 to Page 19, Line 7; Page 19, Line 15 to Page 20, Line 14). The specification also describes "dicoumarol, a ZC inhibitor, disrupts increased glutaminase production during chronic inflammation" and figure 15 illustrates it (Page 13, Lines 8-11). However, in said Figure the glutaminase concentration or production thereof is not even shown.
> Thus, specification as currently presented ... does not provide information on inhibition of glutaminase enzyme production by said step, nor said effect is achieved through oral administration for said glutaminase inhibitor.

Applicant respectfully traverses the rejection for the reasons stated herein below.

First, the Examiner is completely incorrect in his assertion that the specification does not provide information on alleviation of chronic pain in the peripheral nervous system via *inhibition of glutaminase enzyme production*. The use of an inhibitor of glutaminase enzyme production to alleviate chronic pain in the peripheral nervous system is clearly described and enabled by the specification of the subject application, as described in detail below.

The term "glutaminase inhibitor", as recited in the currently pending claims, is clearly defined in the specification to include both inhibitors of glutaminase enzyme activity and glutaminase enzyme production, as defined in paragraphs [0044]-[0045] of the Specification. Indeed, Figure 2 demonstrates mechanisms involved in the inhibition of glutaminase enzyme production. One of the molecules considered to be involved in this mechanism is ZC. Figure 14 and Paragraphs [0031] and [0071] of the Specification illustrate that glutaminase production is regulated by ZC, and that ZC levels are modified during chronic inflammation. "These results are consistent with ZC's role as a stabilizer of glutaminase mRNA during times of cellular stress. Increased production of ZC during inflammation appears important for stabilization of glutaminase mRNA and elevated glutaminase production." Thus,

an inhibitor of ZC would be considered to also function as an inhibitor of glutaminase production.

Therefore, the ability of an inhibitor of ZC to inhibit glutaminase production and alleviate chronic pain in response to increased glutaminase production was tested, as shown in Figures 15-16 and as described in detail in Paragraphs [0032]-[0033] and [0072]-[0073] of the Specification.

First, Figure 15 and Paragraphs [0032] and [0072] illustrate that dicoumarol, an inhibitor of ZC, was able to alleviate chronic pain in a rat inflammation model. Next, the mechanism of action of dicoumarol was evaluated, as shown in Figure 16 and described in paragraphs [0033] and [0072]-[0073]. The DRG's from rats utilized in the study shown in Figure 15 were collected and ***processed for expression levels of ZC and glutaminase***, and the results of such expression study are shown in ***Figure 16***. It is clearly evident that increased glutaminase production is observed during inflammation, and that the administration of dicoumarol resulted in a decrease in glutaminase enzyme production to a level similar to that seen in control rats not experiencing inflammation. Therefore, the Examiner's assertion that "glutaminase concentration or production thereof is not even shown" is completely false.

Further, the Specification also provides a greater discussion on the prevention of increased glutaminase production in paragraphs [0079]-[0081] of the Specification, providing even further disclosure of the inhibition of glutaminase enzyme production in response to chronic pain.

Therefore, the Specification has ***more than adequately described and fully enabled*** the use of an inhibitor of glutaminase enzyme production to alleviate chronic pain in the peripheral nervous system. The *in re Wands* factors regarding undue experimentation raised by the Examiner are therefore irrelevant, as **absolutely no** experimentation is required to practice the invention.

Further, the claims of the subject application actually recite the use of at least one inhibitor of neurotransmitter synthesis selected from glutamine synthetase inhibitor, a glutamate dehydrogenase inhibitor, a pyruvate carboxylase inhibitor, a glutamine cycle inhibitor, a glial cell tricarboxylic acid cycle inhibitor, and combinations thereof. Support for this claim limitation is more than adequately provided in Figures 17-24 and Paragraphs [0034]-[0041], [0045] and [0090]-[0110] of the Specification.

In the second 35 U.S.C. 112, ¶1 rejection (set forth in #15 on Page 6 of the Office Action), the Examiner also stated that the Specification does not

disclose oral administration of glutaminase inhibitors. Applicant respectfully traverses the Examiner's assertion.

Paragraph [0046] of the Specification states that "[w]hile the initial experiments described herein have utilized injection of an inhibitor of neurotransmitter synthesis, the inhibitor of neurotransmitter synthesis should also be amenable to topical or oral application". Applicant respectfully submits that it is clearly within the skill of a person having ordinary skill in the art to adapt an injectable drug for use in oral applications, and that a large knowledge base in the study of pharmacology would provide a vast amount of guidance, as well as an unlimited number of working examples to enable such adaptation without requiring undue experimentation to practice the presently claimed invention. Indeed, oral administration of some of the inhibitors of neurotransmitter synthesis described and claimed herein is already utilized. Therefore, Applicant respectfully submits that oral administration of inhibitors of neurotransmitter synthesis is fully described and enabled by the present application, and that undue experimentation would not be required to practice the presently claimed invention.

Thus, for the reasons stated herein above, Applicant respectfully submits that claims 1, 3-11, 19 and 21-23 meet the written description and enablement requirements of 35 U.S.C. 112, ¶1. Applicant respectfully requests

reconsideration and withdrawal of the 35 U.S.C. 112, ¶1 rejection(s) of the claims.

Applicant's Response to the 35 U.S.C. 112, ¶2 Rejection

In the Office Action, the Examiner rejected Applicant's claims 3 and 21 under 35 U.S.C. 112, ¶2. In support thereof, the Examiner stated that such claims incorrectly depend from canceled claims, and also recite the term "derivatives" that the Examiner considers to be indefinite.

In response thereto, the dependency of claims 3 and 21 has been amended herein. Applicant respectfully traverses the rejection with regards to the term "derivatives"; however, in order to expedite issuance of a patent from the subject application, Applicant has amended the claims to remove such term.

Therefore, Applicant respectfully submits that claims 3 and 21 are definite and particularly point out and distinctly claim that which Applicant regards as the invention. Applicant respectfully requests reconsideration and withdrawal of the 35 U.S.C. 112, ¶2 rejection of claims 3 and 21 as now amended.

Applicant's Response to the 35 U.S.C. 103(a) Rejection

In the Office Action, the Examiner rejected Applicant's claims 1, 3-11, 19 and 21-23 under 35 U.S.C. 103(a) as being obvious over the combined

teachings of Rosenberg (US 5,158,976) with evidence provided by Melzack et al. (1965) and further in view of Fujimoto et al. (US 6,291,523). Applicant respectfully traverses the rejection for the reasons stated herein below.

Claims 1 and 3-11 of the subject application are directed to methods for alleviating chronic pain in a subject by administering an effective amount of at least one inhibitor of neurotransmitter synthesis to a subject suffering from chronic pain at a **peripheral nervous system inflammation site**, wherein the administration results in **inhibition in synthesis of at least one neurotransmitter in the *peripheral nervous system*** of the subject at the peripheral nervous system inflammation site. This results in a reduction in **glutamate stimulation of peripheral sensory nerve fibers**. The at least one inhibitor of neurotransmitter synthesis is selected from the group consisting of a glutamine synthetase inhibitor, a glutamate dehydrogenase inhibitor, a pyruvate carboxylase inhibitor, a glutamine cycle inhibitor, a glial cell tricarboxylic acid cycle inhibitor, and combinations thereof.

Claims 19 and 21-23 are directed to methods of alleviating acute and chronic pain by administering a combination of the at least one inhibitor of neurotransmitter synthesis (as described herein above) and at least one compound having analgesic effects.

Rosenberg does not teach, disclose or even suggest the presently claimed invention for several reasons, as outlined in detail herein below.

First, Rosenberg teaches the use of inhibitors of enzymatic conversion of gluatmine to glutamate in the **central nervous system** to inhibit neuronal injury and death. However, the effects of glutamate on the central nervous system and the peripheral nervous system are sharply different and unrelated. In the central nervous system, increased extracellular glutamate concentrations have pathological effects that can result in **neuronal injury and death**. This is in sharp contrast to the effects of glutamate on peripheral sensory nerve fibers in the **peripheral nervous system**, where increased levels of glutamate act as a **sensitizer, NOT a neurotoxin**. Therefore, the teachings of Rosenberg regarding the central nervous system are not applicable to the presently claimed invention, which is related to the peripheral nervous system.

Second, Rosenberg does not teach, disclose or even suggest the use of any of the inhibitors of neurotransmitter synthesis recited in the claims of the subject application, namely, a glutamine synthetase inhibitor, a glutamate dehydrogenase inhibitor, a pyruvate carboxylase inhibitor, a glutamine cycle inhibitor, and a glial cell tricarboxylic acid cycle inhibitor.

Third, the Examiner refers to Column 7, Lines 34-51 as teaching that "effect of said inhibitors is tested *in vivo* to evaluate the effect of said inhibitors

in subjects having neuronal-injury related conditions via evaluating the effects on peripheral sites through histological examination". However, upon a full reading of the Rosenberg reference, it is clear that this examination is actually to examine that the inhibitor had **NO** lasting effect on peripheral tissues, and the Rosenberg reference actually teaches the administration of a second agent to **PREVENT ANY LASTING EFFECT ON PERIPHERAL TISSUES**. See for example, Column 2, lines 16-35, which clearly state that "to **ameliorate** the effect of the inhibitor on peripheral tissue..." (emphasis added).

The Examiner also points to Column 8, Lines 27-33 of Rosenberg as teaching spinal tap as a "means of administering a therapeutic agent at a peripheral inflammation site"; again, however, this administration is simply a mechanism by which the agent is **delivered to the central nervous system**, and Rosenberg provides no evidence that this site is actually a peripheral nervous system inflammation site. For example, such citation from Rosenberg also teaches administration of the drug orally or intranasally: does this mean that the mouth or nose are peripheral nervous system inflammation sites? Obviously not.

The Examiner has recognized the deficiencies of Rosenberg and has attempted to supply such deficiencies with the teachings of Melzack et al. In particular, the Examiner states that: "note that nociceptive pain behavior is a

manifestation of neuronal injury" (Office Action, Page 8, paragraph 2). However, it is known to a person having ordinary skill in the art that chronic pain is not necessarily the result of neuronal injury and death in the **central nervous system**. In fact, injury to the central nervous system often leads to a **loss** of or **diminished** sensation, including pain, rather than an increase in pain. Therefore, neuronal injury and chronic pain cannot be equated.

For example, many types of neuronal injuries in the central nervous system, such as those associated with Alzheimer's disease as well as stroke, are NOT associated with chronic pain, and simply stating that neuronal injury and death MIGHT result in pain does not provide a correlation that would lead a person of ordinary skill in the art to associate ANY neuronal injury or death with chronic pain (especially when it is known that injury to the CNS often leads to a ***decrease or loss*** **of pain**), and thus suggest to a person of ordinary skill in the art that a method of preventing neuronal injury MUST also alleviate chronic pain. This type of suggestion is clearly incorrect. Rather, without some teaching that a neuronal injury actually results in a chronic pain response, a reference related to preventing said neuronal injury cannot be utilized in an obviousness rejection of a claim related to alleviating chronic pain. The Melzack reference is clearly related to pain in response to exposure of skin or peripheral nerve fibers to causative agents, and thus such reference provides no teaching,

suggestion, motivation, or reasonable expectation of success that a neuronal injury in the central nervous system will result in chronic pain.

The Examiner has further attempted to supply the deficiencies of Rosenberg with the teachings of Fujimoto et al. Fujimoto et al. is directed to antiinflammatory agents that are COX-2 selective cyclooxygenase inhibitors and are useful for the treatment of pain associated with cyclooxygenase-2 dependent disorders. These agents function in the same manner as known compounds such as aspirin, CELEBREX®, VIOXX® and the like, by inhibiting prostaglandins, which are inflammatory mediators. However, contrary to the Examiner's assertion, the agents of Fujimoto et al. do not affect neurotransmitter synthesis. In addition, Fujimoto et al. do not teach, disclose or even suggest that phenyl acetic acid is an inhibitor of neurotransmitter synthesis, but simply teach that phenyl acetic acid is an inhibitor of COX-2. Therefore, the teachings of Fujimoto et al. add nothing to the fact that Rosenberg does not teach, disclose or even suggest a method for alleviating chronic pain in a subject by administering an effective amount of at least one **inhibitor of neurotransmitter synthesis** to a subject suffering from chronic pain at a **peripheral** site of inflammation, thereby resulting in **inhibition of at least one neurotransmitter** in the **peripheral** nervous system of the subject

at the peripheral site of inflammation, resulting in **a reduction in *glutamate stimulation of peripheral sensory nerve fibers***.

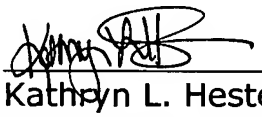
Therefore, Applicant respectfully submits that claims 1, 3-11, 19 and 21-23 are non-obvious over such combination of references. Applicant respectfully requests reconsideration and withdrawal of the 35 U.S.C. 103(a) rejection of the claims as currently pending.

## CONCLUSION

This is meant to be a complete response to the Office Action mailed June 6, 2007. Applicant respectfully submits that each and every rejection of the claims has been overcome. Further, Applicant respectfully submits that claims 1, 3-11, 19 and 21-23 are patentable over the art of record and are now in a condition for allowance. Favorable action is respectfully solicited.

Should the Examiner have any questions regarding this Amendment, or the Remarks contained therein, Applicant's representative would welcome the opportunity to discuss the same with the Examiner.

Respectfully submitted,



Kathryn L. Hester, Ph.D.
Registration Number 46,768
DUNLAP, CODDING and ROGERS, P.C.
Customer No. 30589
P.O. Box 16370
Oklahoma City, Oklahoma 73113
Telephone:(405) 607-8600
Facsimile:(405) 607-8686
E-Mail: kathryn_hester@okpatents.com
Web Site: www.okpatents.com

Agent for Applicant